REMARKS

Applicants have amended Claims 15, 17, 30, 32, 33, and 46. The amendments add no new matter and are fully supported by the specification and claims as originally filed.

Pending Claims 15-46 are currently presented for examination. Applicants respond below to the specific rejections set forth in Office Action dated May 7, 2008. For the reasons set forth below, Applicants respectfully traverse.

Rejection Under 35 U.S.C. § 102(b)

Berg *et al.*

The Examiner has rejected Claims 15-18, 23-29, 32-34 and 39-45 under 35 U.S.C. 102(b) as allegedly being anticipated by Berg *et al.* (WO 02/18635, March 2002, hereinafter "Berg"). Applicants respectfully traverse.

The teachings of Berg do not meet each and every limitation of Claims 15 and 32, or claims that depend therefrom. As amended, Applicants' claims require the step of "providing an internal control reagent selected from the group consisting of cells, parasites, cells comprising organelles, cells comprising viral particles, cells comprising parasites, cells comprising bacterial cells and any combination thereof..." Thus, the claimed subject matter is currently directed toward methods that use **viable** internal control reagents.

In the present application, Applicants have discovered, for example, that viable reagents (e.g., cells, parasites, cells comprising organelles, cells comprising viral particles, cells comprising parasites, cells comprising bacterial cells or any combination thereof) can be used as internal controls in methods used to verify the efficiency of sample preparation and the performance of nucleic acid amplification and/or detection after sample preparation. For instance, Applicants have demonstrated in working Examples 1 and 2 that the viable reagents, *Escherichia coli* cells and *Bacillus globigii* spores, could serve as effective internal controls. As described in the instant application, the use of viable internal control reagents provides significant advantages over the use of non-viable internal control reagents. One advantage of using a viable reagent as an internal control is that it "better reflects the conditions of the tested sample." Specification at Pg. 39, lines 5-7. Furthermore, the use bacterial endospores (e.g., *B. globigii* spores), in particular, provides the added advantage of "providing a universal control for

microbial cell lysis since bacterial spores are among the most difficult cells to lyse." Specification at Pg. 46, lines 4-8.

In contrast to Applicants' teachings relating to the use of **viable** internal control reagents, Berg describes "the use of **non-viable** particles containing an internal control nucleic acid sequence in nucleic acid-based analysis." Berg at Pg. 1, lines 4-6. Berg defines a non-viable particle as an "entity which is capable of encapsulating, entrapping or embedding an internal control nucleic acid but which is not capable of propagation either alone (i. e. by self propagation) or by culture in a biological system which would normally allow the propagation of the entity in question." Berg at Pg. 18, lines 14-19. According to Berg, typical non-viable particles are liposomes, protein particles, and viral particles. Berg at Pg. 18, lines 20-21 and 28-29. Accordingly, Berg does not teach the use of a viable internal control reagent, such as *E. coli* cells or *B. globigii* spores, as required by Applicants' amended claims.

In addition, the Examiner states that Berg teaches that the test sample including the target nucleic acid "may be derived from cultured cells, bacteria or viral particles (*in vitro* source) or from human, plant or animal sources (*in vivo* sources)." The Examiner further states that Berg teaches "the target nucleic acid include cells, derived from multicellular organisms or unicellular organisms as well as viruses and bacteriophages." (Office Action at Pgs. 3-4). Applicants disagree. "Target nucleic acids," in the context of Applicants' claims refer only to IC target nucleic acids. Berg stresses that the IC nucleic acids are non-viable; as such the target nucleic acids cannot include viable organisms, as the Examiner suggests. In other words, although the test sample taught by Berg can be derived from viable sources, the internal control reagent taught by Berg refers only to a non-viable reagent, as described above. As such, Berg does not teach the use of viable internal control reagents, as required by Applicants' claims.

Because Berg do not teach every element Claims 15-18, 23-29, 32-34 and 39-45, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 102(b).

Rejections Under 35 U.S.C. § 103(a)

Claims 19-21, 31 and 35-37

The Examiner has rejected Claims 19-21, 31 and 35-37 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Berg as applied above in view of Ke *et al.* (Clinical Chemistry,

46(3):324-331 (2000), hereinafter "Ke") and Kuske *et al.* (Applied and Environmental Microbiology, 64(7):2463-2472 (1998), hereinafter "Kuske"). The Examiner alleges that Berg teach each and every limitation of Claims 19-21, 31 and 35-37, including "an internal control reagent that comprises cells from a bacterial origin" (Office Action at 6), but does not teach the use of *E. coli* cells or *B. globigii* spores as internal control reagents, which Ke and Kuske teach. The Examiner argues that it would have been *prima facie* obvious for one skilled in the art to carry out the claimed methods using different cell types isolated from different sources. Applicants respectfully traverse.

As an initial matter, as discussed in reference to the rejection under 35 U.S.C. § 102(b), Berg teaches internal control reagents that must be non-viable. Accordingly, Berg does not teach "an internal control reagent that comprises cells from a bacterial origin," as the Examiner suggests.

Regarding Ke, the Examiner states that Ke teaches an "internal control reagent" that "comprises cells derived from *E. coli*". Office Action at pgs. 6-7. The Examiner points to the section of Ke entitled "construction of the internal control" at page 325, col. 2 as well as Table 1. This section entitled "construction of the internal control" states:

> CONSTRUCTION OF THE INTERNAL CONTROL
> An internal control was constructed essentially as described previously by Rosenstraus et al. (*21*). A 252-bp DNA fragment consisting of a 206-bp sequence not found in GBS flanked by the sequences of each of the two GBS-specific primers was used as a template for the internal control. This fragment was cloned into the pCR2.1 vector (Invitrogen). The **recombinant plasmid**, named pSTB, was **isolated** from transformed *Escherichia coli* by the Qiagen plasmid mini kit (Qiagen). The **purified plasmid** was then **linearized** with *Eco*RI (New England Biolabs) and serially diluted. The concentration of the linearized plasmid was optimized to permit amplification of the **252-bp internal control product** without significant detrimental effect on the GBS-specific amplification.

Accordingly, Ke does **not** teach an internal control that comprises **cells** derived from *E. coli.* Rather, the internal controls used in Ke are **isolated, purified recombinant plasmids** that have been linearized. In the construction of the internal control taught by Ke, *E. coli* are simply used to amplify a plasmid that is subsequently isolated from the *E. coli*, purified, and linearized.

The Examiner further states that Ke teaches an "internal control reagent" that "comprises cells derived from bacterial spores such as *Bacillus anthracis* (Table 1)". Office Action at pg. 7.

However, Table 1 is not list of internal control reagents that are added to a sample containing target nucleic acids. As stated in Ke:

> The specificity of the conventional PCR assay was verified using purified genomic DNA (0.1 ng/reaction) from a battery of ATCC reference strains representing 105 aerobic and 18 anaerobic bacterial species as well as 2 fungal species (Table 1)

Accordingly, the reagents listed in Table 1 of Ke were not used in methods to verify the efficiency of sample preparation and the performance of nucleic acid amplification and/or detection after sample preparation, as encompassed by Applicants' claims. Rather, the purified genomic DNA from these reference strains were used to determine the specificity of the PCR assay performed in Ke.

Regarding Kuske, the Examiner states that Kuske teaches an "internal control reagent" that "comprises cells derived from *Bacillus globigii.*" Kuske describes seeding soil with *Bacillus globigii* endospores. The nucleic acids are extracted from the seeded soil (test sample), and PCR is used to detect the *B. globigii* test sample nucleic acids. (Kuske, pgs. 2464-65, "Materials and Methods" section). To control for the amplification procedure, Kuske teaches the addition of **purified DNA** to the purified nucleic acids of the test sample. (Kuske, pg. 2466, col. 1, "PCR assays to detect specific microbial targets" section). Accordingly, Kuske does **not** teach an internal control that comprises **cells** derived from *B. globigii.* Rather, the internal control taught by Kuske is purified DNA.

Applicants note that the internal controls that are added to the samples in Ke and Kuske are **not** a "cell, a parasite, a cell comprising an organelle, a cell comprising a viral particle, a cell comprising a parasite, a cell comprising a bacterial cell and any combination thereof having at least one internal control (IC) nucleic acid target sequence therein," as required by Applicants' claims. Accordingly, neither Ke nor Kuske teach the use of a viable internal control reagent. Because Berg, in combination with either Ke or Kuske, does not teach or suggest each and every element of Claims 19-21, 31 and 35-37, the references fail to establish that Claims 19-21, 31, and 35-37 are *prima facie* obvious under 35 U.S.C. § 103(a).

Furthermore, the Applicants note that Claims 19-21, 31, and 35-37 ultimately depend from either independent Claim 15 or independent Claim 32. Applicants assert that the PTO has failed to establish a *prima facie* case of obviousness or that Berg discloses the invention of Claims 15 and 32 as amended, for at least the reasons discussed above. Thus, even if Ke and

Kuske did teach the use of *E. coli* cells or *B. globigii* spores as internal control reagents, a point Applicants do not concede, the addition of these elements to Berg does not cure the deficiencies of Berg noted above.

Applicants therefore respectfully request that, for at least these reasons, the PTO reconsider and withdraw the rejection of Claims 19-21, 31 and 35-37 as obvious over Berg in light of Ke and Kuske.

Claims 30 and 46

The Examiner has rejected Claims 30 and 46 as being unpatentable over Berg in view of Picard and Bergeron (Drug Discovery Today, 7(2):1092-1101 (2002), hereinafter "Picard"). The Examiner alleges that Berg teaches each and every limitation of Claims 30 and 46 but does not teach a sample preparation procedure comprising the steps of nucleic acid extraction and elimination, neutralization and/or inactivation of nucleic acid testing (NAT) inhibitors, which Picard teaches. Applicants respectfully traverse.

Applicants note that claims 30 and 46 ultimately depend from independent Claim 15. Applicants assert that the PTO has failed to establish a *prima facie* case of obviousness or that Berg disclose the invention of Claims 15 as amended, for at least the reasons discussed above. Thus, even if Picard did teach nucleic acid extraction and elimination, neutralization and inactivation of NAT inhibitors, a point Applicants do not concede, the addition of these elements to Berg does not cure the deficiencies of Berg noted above.

Applicants therefore respectfully request that, for at least these reasons, the PTO reconsider and withdraw the rejection of Claims 30 and 46 as obvious over Berg in light of Picard.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, the Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. The Applicants reserve the right to pursue at a later date any previously pending or

other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that the Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

CONCLUSION

In view of the above amendments and remarks, Applicants respectfully maintain that the claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: NOV. 6, 2008

By: Kathleen Mekjian

Kathleen R. Mekjian
Registration No. 61,399
Attorney of Record
Customer No. 20,995
(619) 235-8550